LIVER FUNCTION AS INFLUENCED BY ANESTHETICS AND NARCOTICS.*

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The functional capacity of the liver may be estimated by means of phenoltetrachlorphthalein. This drug when given intravenously in a normal dog will be excreted solely in the bile and can be recovered from the feces. The output of normal dogs is fairly constant, and the upper and lower limits of excretion may be placed at 65 and 45 per cent., respectively. A normal dog under uniform conditions gives a constant output and rarely varies more than 10 per cent. between the limits of 65 and 45 per cent.

In earlier publications[1,2] we have reported experiments to show that phenoltetrachlorphthalein is removed from the body fluids by the activity of the hepatic epithelium and escapes with the bile into the intestinal tract. Any poison which injures the hepatic epithelium (chloroform, phosphorus, hydrazin) will cause a drop in the output of phthalein, and this fall in the phthalein curve will be proportional to the amount of liver injury. In severe liver injury the phthalein output may fall to zero. Injury of the liver by actual cautery will cause a fall in the phthalein output, depending upon the tissue destroyed and the inflammatory reaction. Given an actual injury of the liver cell, it will be noted that the phenoltetrachlorphthalein appears in the urine in demonstrable quantities, even 1 to 10 per cent. This is never demonstrated in normal animals.

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[1] Whipple, G. H., Mason, V. R., and Peightal, T. C., *Bull. Johns Hopkins Hosp.*, 1913, xxiv, 207.

[2] Whipple, G. H., Peightal, T. C., and Clark, A. H., *Bull. Johns Hopkins Hosp.*, 1913, xxiv, 343.

After a liver injury by means of chloroform the liver may repair its injured cells and form new ones. At this time the phthalein excretion may rise above normal, indicating perhaps that the new cells are more active. The same indication of hyperactivity may be noted after small doses of hepatic poisons, which may have an irritant effect or actually stimulate the liver cells. Hyperactivity is quite distinct in the condition of tetany brought about by removal of the parathyroid glands.[3]

Vascular disturbances may so modify the environment of the liver cell as to cause various degenerations; for example, fatty degeneration in passive congestion. In experimental passive congestion the phthalein output may show a diminution depending upon the severity of the passive congestion. The Eck fistula which shunts the portal blood around the liver and reduces the blood circulating through the liver to about one-third normal, will modify the excretion of phenoltetrachlorphthalein.

The ductless glands modify the functional activity of the liver, as pointed out in a recent publication. Pancreatic extirpation is followed by a falling curve of phthalein excretion which may go as low as one-third normal. This indicates that the pancreas is essential for proper liver function and suggests that the pancreas may have an accelerating influence on the liver.

Adrenal insufficiency is accompanied by a fall in the phthalein excretion, and with hypertrophy of the remaining adrenal fragment the liver excretion returns to normal.

Hypophysis extirpation is followed by minor fluctuations in the phthalein curve with a final drop which takes place shortly before the drop in body temperature which precedes the fatal outcome.

Thyroid removal causes no change in phthalein excretion. Parathyroid extirpation with tetany is associated with a maximum excretion of phenoltetrachlorphthalein, and in many instances evidence of hyperexcretion and abnormal activity of the liver cells. We may assume that in the condition of parathyroid tetany the liver cells are acted on by some powerful stimulus,—that in this condition they remove the phthalein from the blood and pour it into the intestine very promptly. In fact, the liver output will almost

[3] Whipple, G. H., and Christman, P. W., *Jour. Exper. Med.*, 1914, xx, 297.

equal the amount recovered from the feces after mouth feeding, almost a quantitative elimination of the drug through the liver.

All these experiments show how accurate an index of liver activity is the excretion of phenoltetrachlorphthalein. As experimental evidence accumulates we learn to place more and more confidence in this drug as an indicator of hepatic activity. The experiments given below show that ether anesthesia given over a period of two hours may cause interference with liver function lasting over a period of twenty-four hours after the anesthesia. There is no comparison, of course, with the injury done by chloroform anesthesia, which causes actual liver necrosis and much greater impairment of liver function.

Paraldehyde in sufficient amounts to produce stupor usually causes a drop in the phthalein curve. Chloral and urethane give very similar results. Small doses may cause no depression, but rather a maximum output, suggesting that small doses may actually stimulate the liver cells.

Alcohol in large doses sufficient to produce stupor for several hours causes a depression of the phthalein excretion and indicates a definite injury to the liver cells. That the liver at this time might be more susceptible to various injurious agents, for example bacteria, seems highly probable.

When phthalein injection gives evidence of a depression of liver activity to two-thirds or one-half normal, we may assume a very definite interference with liver activity. A depression of this amount may be found in an Eck fistula liver, or in one handicapped by passive congestion, or even in one injured by phosphorus or hydrazin. This comparison shows that the injury done the liver by these anesthetics and narcotics, although temporary, is really definite and worthy of consideration.

METHOD.

The method used has been described in a recent publication,[4] and in fact these experiments were done at that time with a great number of control experiments. The references given[5,6,7] cover all the points concerning the prep-

[4] Whipple and Christman, *loc. cit.*

[5] Whipple, Peightal, and Clark, *loc. cit.*

[6] Rowntree, L. G., Hurwitz, S. H., and Bloomfield, A. L., *Bull. Johns Hopkins Hosp.*, 1913, xxiv, 327.

[7] Whipple and Christman, *loc. cit.*

aration of the drug for injection, the extraction of the feces, and the general control and conduct of the experiments.

EXPERIMENTAL OBSERVATIONS.

ETHER ANESTHESIA.

Dog 13–1.—Young mongrel, male; weight 14 pounds.

Oct. 23. Phthalein 0.16 gm. intravenously.

Oct. 24. Abundant feces. Phthalein excretion 48 per cent.

Oct. 30, 11 A. M. Ether anesthesia 2 hours. At the end of the anesthesia phthalein 0.1 gm. given intravenously. Urine shows a trace of phthalein.

Oct. 31. Abundant feces. Phthalein excretion 26 per cent.

Nov. 6. Phthalein 0.1 gm. intravenously. Urine contains no phthalein.

Nov. 8. Formed feces. Phthalein excretion 44 per cent.

ETHER ANESTHESIA.

Dog 12–104.—Small fox-terrier, male; weight 15¾ pounds.

Oct. 30, 1 P. M. Phthalein 0.1 gm. intravenously.

Oct. 31. Abundant feces. Phthalein excretion 49 per cent.

Jan. 15, 3 P. M. Ether anesthesia 2 hours. At the end of the anesthesia phthalein 0.1 gm. given intravenously.

Jan. 17. Abundant feces. Phthalein excretion 39 per cent.

ETHER. ALCOHOL. CHLOROFORM.

Dog 13–55.—Strong bulldog, male; weight 23 pounds.

Jan. 20. Phthalein 0.2 gm. intravenously.

Jan. 21. Abundant feces. Phthalein excretion 66 per cent.

Feb. 4. Light ether anesthesia 2 hours. At the end of the anesthesia phthalein 0.2 gm. given intravenously.

Feb. 5. Abundant feces. Phthalein excretion 63 per cent.

Feb. 11. Ether anesthesia 2 hours; deeper anesthesia than before. At the end of the anesthesia 0.2 gm. phthalein given intravenously.

Feb. 12. Urine shows a trace of phthalein; no feces.

Feb. 14. Abundant feces. Phthalein excretion 53 per cent.

Feb. 18, 10 A. M. Dog given 50 c.c. of 95 per cent. alcohol by stomach tube. This caused much intoxication, but dog was able to walk a little. 5 P. M. Dog recovering from intoxication. Phthalein 0.2 gm. intravenously.

Feb. 20. Some difficulty with purgation. Phthalein excretion 60 per cent.

Apr. 21. Chloroform anesthesia 1 hour.

Apr. 22. Phthalein 0.2 gm. intravenously. Urine contained much phthalein (7 per cent.).

Apr. 24. Abundant feces. Phthalein excretion 31 per cent.

The preceding experiments show that ether anesthesia for two hours may cause a temporary decrease in hepatic secretion and elimination of phenoltetrachlorphthalein. It is to be kept in mind that the phthalein is injected at the end of the period of anesthesia

and its excretion takes place during the following twenty-four hours. The evidence shows that the injury done by the drug affects the functional capacity of the liver for the twenty-four hours subsequent to the anesthesia. There is no histological evidence of liver injury, but we have shown elsewhere that this physiological test is more sensitive than any estimate based on histological evidence. Ether anesthesia for one hour will scarcely cause any evidence of depressed liver function, and in many instances a two hour light surgical anesthesia will not cause any depression in the phthalein curve of a strong dog.

Ether anesthesia causes a small amount of phthalein to appear in the urine, which speaks in favor of a slight actual injury to the liver parenchyma. It is seen in the preceding experiment that a large amount of phthalein escapes in the urine after a chloroform anesthesia, which is known to cause outspoken central liver necrosis. It has been shown in earlier communications that injury of the liver cell is responsible for a modification of the phenoltetrachlorphthalein, which permits it to pass the kidney filter. We may assume then that there is in all probability a slight injury produced in the liver cells by two hours of ether anesthesia.

PARALDEHYDE.

Dog 13–50.—Young terrier, male; weight 14¾ pounds.

Jan. 17. Dog has distemper, but is in fair condition. 11 A. M. Paraldehyde 6.5 c.c. given by stomach tube. 11.30 A. M. Dog is reeling about cage in wild excitement. 1 P. M. Periods of excitement and again of stupor. Phthalein 0.1 gm. intravenously and paraldehyde 1 c.c. given by stomach tube. 2.30 P. M. Dog much intoxicated and disoriented. 4.30 P. M. Condition unchanged.

Jan. 18, 11 A. M. Dog recovered from drug. Urine shows only a faint trace of phthalein.

Jan. 19. Abundant feces. Phthalein excretion 33 per cent.

Jan. 28. Dog quite sick with distemper and bad diarrhea. Phthalein 0.1 gm. intravenously. Urine shows no phthalein.

Jan. 29. Fluid feces. Phthalein excretion 52 per cent.

PARALDEHYDE.

Dog H–2.—Small mongrel; weight 13½ pounds.

Jan. 8. Phthalein 0.1 gm. intravenously.

Jan. 9. Fluid feces. Phthalein excretion 55 per cent.

Jan. 11. Phthalein 0.1 gm. intravenously. Dog has little distemper and weighs only 12½ pounds. Urine contains no phthalein.

Jan. 12. Abundant feces. Phthalein excretion 54 per cent.

Jan. 20, 12 M. Paraldehyde 5 c.c. by stomach tube. 1 P. M. Anesthesia complete; no period of excitement. Muscular tremors noticeable. 3 P. M. Dog excited and reels about cage. 5 P. M. Dog very noisy and excited, rolls about cage. Phthalein 0.1 gm. intravenously.

Jan. 21. Urine contains much phthalein (0.1 per cent. ±).

Jan. 22. Fluid feces. Phthalein excretion 25 per cent. 3 P. M. Dog given ether and killed.

Autopsy.—The organs are all negative except the liver. Bile passages are normal. Liver shows slight central atrophy and a little fatty degeneration at the edge of the liver lobules. Microscopical section shows a little fatty degeneration of the liver cells, but the nuclei are normal and the fat droplets not numerous. The endothelial cells contain a good deal of yellow pigment.

PARALDEHYDE.

Dog 13–57.—Mongrel fox-terrier; weight 11½ pounds.

Jan. 28, 12 M. Phthalein 0.1 gm. intravenously.

Jan. 29. Abundant feces. Phthalein excretion 58 per cent.

Feb. 10. Phthalein 0.1 gm. intravenously.

Feb. 11. Abundant fluid feces. Phthalein excretion 66 per cent.

Mar. 18, 9.30 A. M. Dog is well. Paraldehyde 5½ c.c. with 4 c.c. of alcohol given by stomach tube. 10.30 A. M. Dog is much intoxicated; salivation marked. 11 A. M. Dog not under anesthetic, but rolls about aimlessly. 4 P. M. Dog out of influence of drug. Phthalein 0.1 gm. intravenously. Urine shows no phthalein.

Mar. 19. Abundant fluid feces. Phthalein excretion 65 per cent.

The three preceding experiments indicate that paraldehyde in doses sufficient for anesthesia causes a lowering of the functional capacity of the liver during the following twenty-four hours. A dose which does not cause anesthesia may or may not cause depression of the liver function. The last experiment shows the maximum excretion of phthalein after a dose of paraldehyde sufficient to cause intoxication for four or five hours.

ALCOHOL.

Dog 13–16.—Strong mongrel, male; weight 21¼ pounds.

Nov. 22. Phthalein 0.2 gm. intravenously.

Nov. 24. Abundant feces. Phthalein excretion 56 per cent.

Dec. 20, 11 A. M. Dog given 50 c.c. of 95 per cent. alcohol by stomach tube. 2 P. M. Dog is intoxicated, but can walk with difficulty. 4 P. M. Dog still intoxicated. Phthalein 0.2 gm. intravenously. At the same time the dog is given 20 c.c. of 95 per cent. alcohol.

Dec. 21. No feces. Urine contains no phthalein.

Dec. 22. Abundant feces. Phthalein excretion 55 per cent.

Jan. 20. Dog is in good condition. Weight 24¾ pounds. 12 M. Dog given

50 c.c. of 95 per cent. alcohol by stomach tube; no food given previously. 12.30 P. M. Dog in stupor and unable to walk. 3 P. M. Dog in stupor and can not be roused. 5 P. M. Dog still deeply intoxicated, but attempts to move. Given 25 c.c. of 95 per cent. alcohol. Phthalein 0.2 gm. intravenously. Urine shows no phthalein.

Jan. 21, 11 A. M. Dog is still somewhat intoxicated and weak.

Jan. 22. Abundant feces. Phthalein excretion 38 per cent.

Mar. 25. Dog is well. 10.30 A. M. Dog given 30 c.c. of 95 per cent. alcohol by stomach tube. 11 A. M. Dog is intoxicated and staggers about cage. 12.30 A. M. Dog is restless and excited. Phthalein 0.2 gm. intravenously. 3 P. M. Recovery almost complete.

Mar. 27. Abundant feces. Phthalein excretion 54 per cent.

ALCOHOL.

Dog 13–29.—Strong bulldog, female; weight 27 pounds.

Dec. 27. Phthalein 0.2 gm. intravenously.

Dec. 29–30. Purgation delayed. Phthalein excretion 48 per cent.

Jan. 7. Phthalein 0.2 gm. intravenously.

Jan. 8. Abundant feces. Phthalein excretion 45 per cent.

Mar. 18, 9.30 A. M. Dog given 50 c.c. of 95 per cent. alcohol by stomach tube. 10.30 A. M. Dog vomited some fluid and alcohol. 10.45 A. M. Dog is drowsy, but not intoxicated. Given 30 c.c. of 95 per cent. alcohol. 11.30 A. M. Dog deeply intoxicated. 4 P. M. Dog still much intoxicated. Given 25 c.c. of 95 per cent. alcohol. Phthalein 0.2 gm. intravenously.

Mar. 19. Dog still somewhat intoxicated and thirsty.

Mar. 20. Abundant feces. Phthalein excretion 28 per cent.

The three preceding experiments show that large doses of alcohol sufficient to cause stupor for a few hours may bring about a decreased phthalein excretion during the twenty-four hours following administration of the drug. Some animals are much more resistant than others and may take large doses without any demonstrable variation in the phthalein curve.

ALCOHOL. URETHANE.

Dog 13–25.—Strong brindle bull, male; weight 21 pounds.

Dec. 18. Phthalein 0.2 gm. intravenously.

Dec. 19. Abundant feces. Phthalein excretion 65 per cent.

Jan. 10. Phthalein 0.2 gm. intravenously.

Jan. 11–12. Little delay in purgation. Phthalein excretion 55 per cent.

Jan. 13, 12 M. Dog given 50 c.c. of 95 per cent. alcohol by stomach tube. 2.30 P.M. Dog pretty much intoxicated. Given 40 c.c. of 95 per cent. alcohol. 3.30 P. M. Dog is deeply intoxicated and lies on side. 4.30 P. M. Vomits fluid and food. 6 P. M. Phthalein 0.2 gm. intravenously. Jan. 15. Abundant feces. Phthalein excretion 44 per cent.

Mar. 25, 10.30 A. M. Dog is well; weight 27 pounds. Given 12 gm. of urethane in water by stomach tube. 11 A. M. Dog excited and intoxicated, but can walk about. 12.30 P. M. Dog intoxicated, but conscious. Given 4 gm. of urethane. Phthalein 0.2 gm. intravenously. 5 P. M. Dog reels about, but is quite active,—not drowsy.

Mar. 26. Urine contains no phthalein.

Mar. 26–27. Fluid feces. Phthalein excretion 64 per cent.

URETHANE. CHLORAL.

Dog 13–17.—Active mongrel, male; weight 16¼ pounds.

Jan. 10. Phthalein 0.1 gm. intravenously.

Jan. 12. Phthalein excretion 61 per cent.

Jan. 20, 12 M. Dog given urethane 7 gm. by stomach tube. 1 P. M. Dog is drowsy and unable to walk. 3 P. M. Dog in stupor; slow respiration, but eyes open. 5 P. M. Urethane 2 gm. by stomach tube. Phthalein 0.1 gm. intravenously.

Jan. 21. Urine contains a definite amount of phthalein. Dog made good recovery and is normal.

Jan. 22. Abundant feces. Phthalein excretion 40 per cent.

Mar. 18, 9.30 A. M. Dog is well; weight 15¼ pounds. Chloral 5 gm. by stomach tube. 10.30 A. M. Deep anesthesia with slow respiration. 4 P. M. Deep anesthesia continues. Dog is quite cool and put on heat pad. Phthalein 0.1 gm. intravenously.

Mar. 19. Dog quite recovered. Urine contains 0.5 per cent. phthalein.

Mar. 20. Abundant fluid feces. Phthalein excretion 32 per cent.

The two preceding experiments indicate that urethane and chloral belong in the same group with alcohol. Their effect upon the liver function, with the excretion of phenoltetrachlorphthalein as an indicator, is identical.

CHLORAL. PREGNANCY.

Dog 13–19.—Strong bulldog, female; weight 30 pounds.

Dec. 6. Phthalein 0.2 gm. intravenously.

Dec. 7. Fluid feces. Phthalein excretion 63 per cent.

Mar. 25, 10.30 A. M. Dog given 4 gm. of chloral by stomach tube. 11.30 A. M. Dog is drowsy and reacts slowly to stimuli. 12.30 P. M. Condition the same. Phthalein 0.2 gm. intravenously. 3 P. M. Dog recovered from effects of drug.

Mar. 27. Abundant feces. Phthalein excretion 67 per cent.

June 10. Dog is in last week of pregnancy. Weight 37 pounds. Phthalein 0.2 gm. intravenously.

June 11. Abundant feces. Phthalein excretion 61 per cent.

This experiment (dog 13–19) shows that a small dose of chloral does not depress liver function and gives some evidence that it may actually stimulate the liver excretion. This is in harmony with

other observations given above and in other papers to the effect that a small dose of a drug may stimulate the liver, whereas a larger dose may injure the liver and depress its functional activity. It is hard to show this point clearly in a normal dog, as the normal output is very close to the maximum output under any condition, and to the amount recovered in the feces after feeding the drug.

CHLOROFORM BY STOMACH.

Dog 13–36.—Young bulldog, female; weight 21 pounds.

Jan. 19. Phthalein 0.15 gm. intravenously.

Jan. 20. Abundant feces. Phthalein excretion 56 per cent.

Jan. 23, 12 M. Chloroform 15 c.c. by stomach tube. 1 P. M. Dog vomited some of the chloroform. 4.30 P. M. Dog given 10 c.c. of chloroform by stomach. No vomiting. 5.30 P. M. Dog curled up quietly and shows no anesthesia.

Jan. 24. Dog quiet and not hungry. Phthalein 0.2 gm. intravenously.

Jan. 26–27. Some delay in purgation. Phthalein excretion 19 per cent.

This experiment (dog 13–36) shows the familiar effect of chloroform upon the curve of phthalein excretion by the liver. There is good evidence of injury done to the liver and interference with its capacity to excrete phenoltetrachlorphthalein. It is possible that the delay in purgation was responsible for a part of the drop in phthalein excretion, but it cannot explain this great drop in excretion which surely was dependent on actual liver injury.

SUMMARY.

It has been established that specific liver poisons (chloroform, phosphorus) which cause histological changes in the liver cells, decrease the liver excretion of phenoltetrachlorphthalein.

Also vascular disturbances (Eck fistula, passive congestion) with or without histological evidence may cause a fall in the output of phthalein through the liver. Sufficient evidence has been brought forward to show that the phenoltetrachlorphthalein excretion is a valuable index concerning the functional capacity of the liver.

Ether anesthesia for a period of two hours usually causes a depression in the phthalein curve during the twenty-four hours following the anesthesia.

Paraldehyde in doses sufficient to give anesthesia and stupor for a few hours will give a definite fall in phthalein excretion.

Chloral and urethane usually cause a decrease in phthalein output when given in considerable amounts.

Alcohol causes a drop in the phthalein curve when given in large doses sufficient to cause stupor for a few hours. The drop in phenoltetrachlorphthalein excretion is demonstrated in the twenty-four hours following administration of the drug. A drop in the phthalein curve to two-thirds or one-half of normal indicates a definite liver injury and temporary impairment of function.